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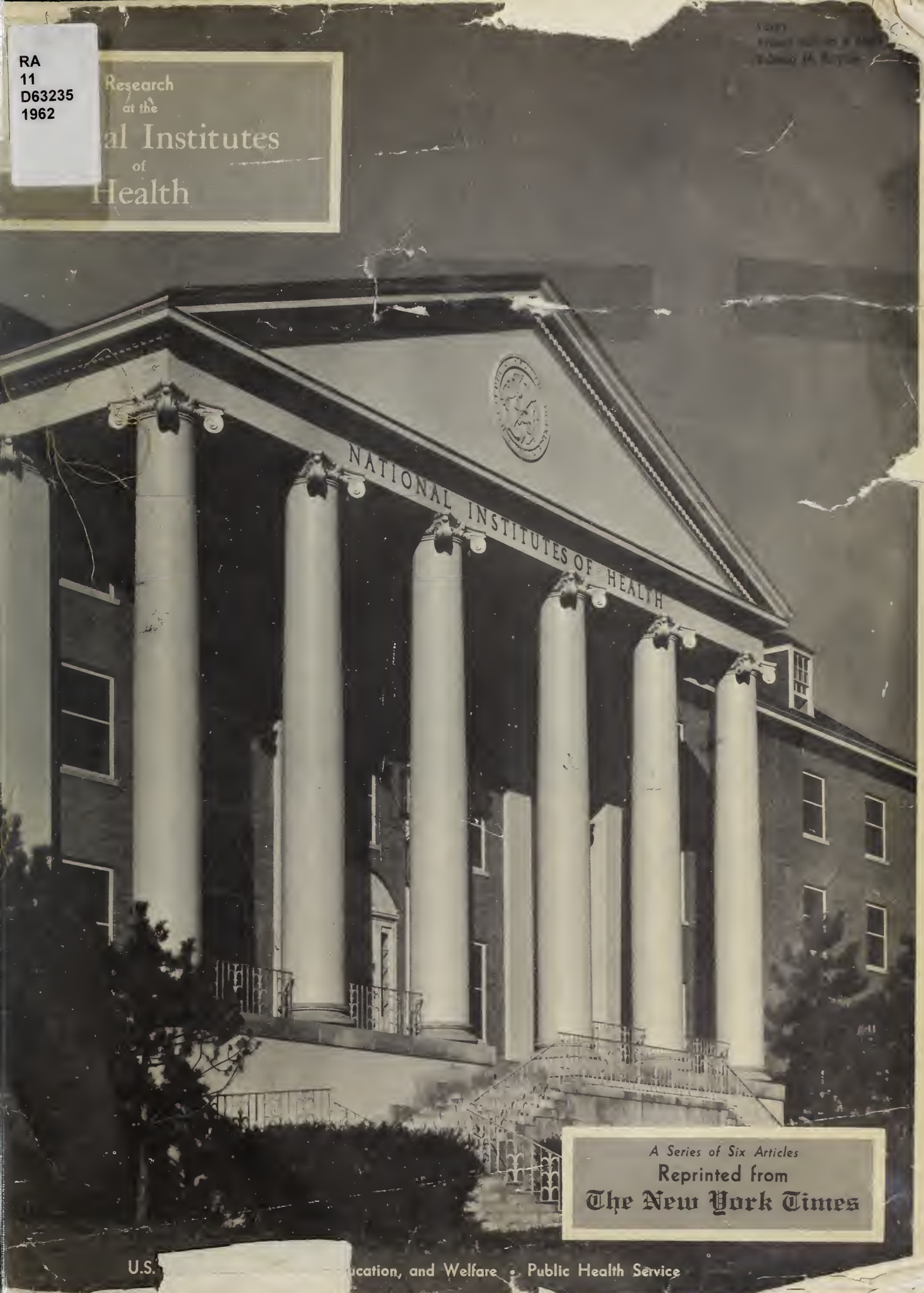
Research at the al Institutes of Health

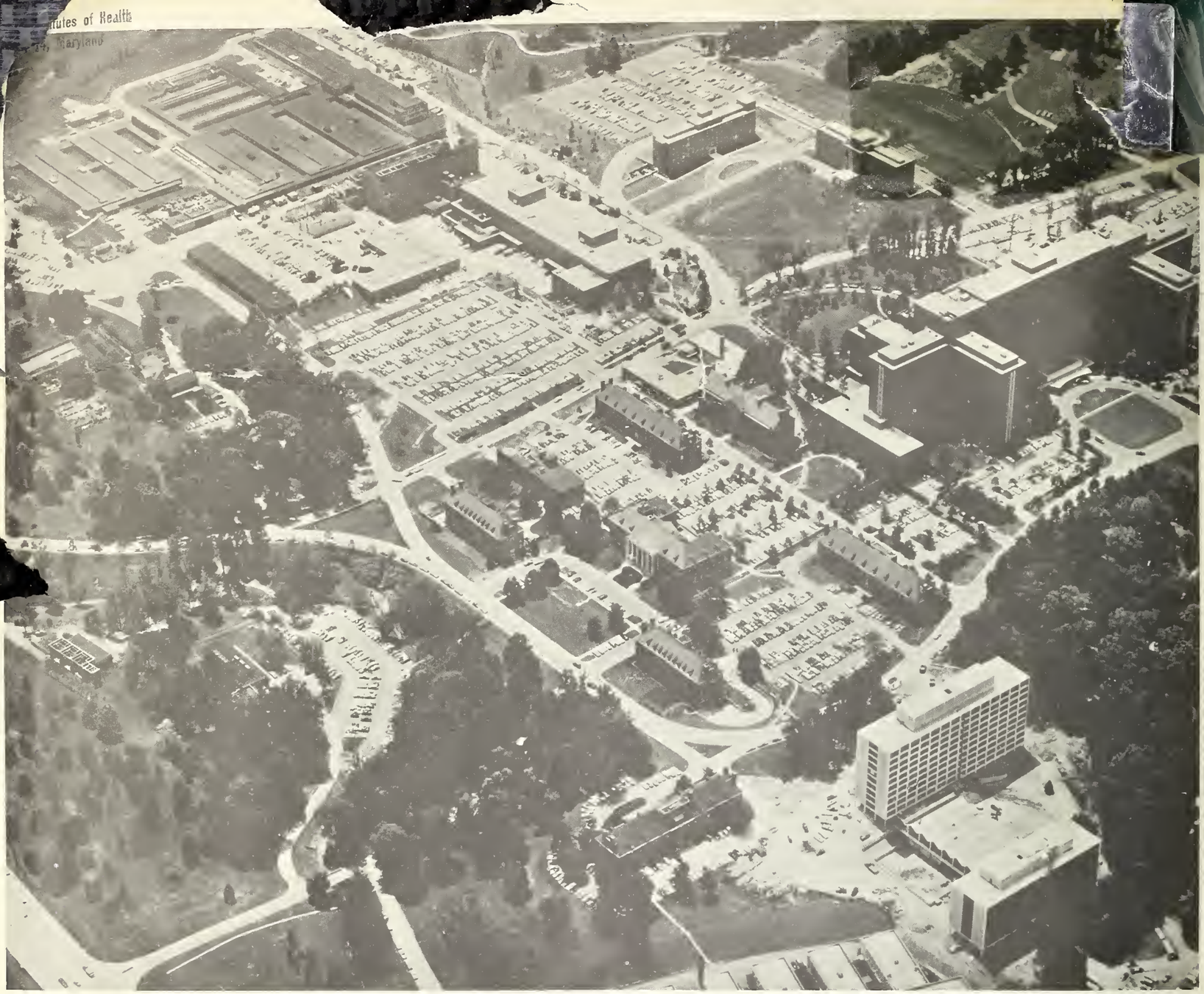


A Series of Six Articles

Reprinted from

The New York Times

U.S. ucation, and Welfare • Public Health Service



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NOTE: With the exception of the two-page photo feature, "Rabbits Aid Medical Research," all of the above articles were originally published in the New York Times and copyrighted by the New York Times Company. They are reprinted herein with the special permission of the copyright owner.

THE COVER—Poised in the center of the "campus" of the National Institutes of Health in suburban Bethesda, Md., about 10 miles from the nation's capitol in Washington, D.C., is Building One, hub of a complex of 42 laboratory, office, hospital and service buildings. With its six gleaming white columns presenting a stately facade, Building One functions as the administrative center of NIH.

ABOVE—This recent panoramic view of the National Institutes of Health covers most of the buildings on its 300 acres of rolling Maryland countryside. Near the center, identifiable by its white columns is Building One, shown close-up on the front cover. Near the upper right corner is the 14-story Clinical Center, and in the lower right corner is the new general office building, officially designated as Building 31. Disposed closely around Building One, in the center, is the original cluster of laboratory buildings.

Introduction

The six articles contained in this publication were written by Harold M. Schmeck, Jr., a reporter for the New York Times, and originally appeared in that newspaper between April 30 and May 21, 1961.

Because they constitute an intelligent layman's objective appraisal of one of the nation's largest medical research centers, this series of articles is reprinted herein with the permission of the New York Times Company. Although the original articles appeared in the news columns of the newspaper, without illustrations, they are here presented in magazine format supplemented with NIH photographs to enhance their informational value. Captions accompanying the photographs, and the text material appearing on pages 10 and 11 are also supplemental to the original articles and are not attributable to the New York Times. The articles themselves, however, are presented exactly as they originally appeared, and in the same sequence.

The National Institutes of Health appreciates the opportunity so kindly extended by the New York Times to reprint the series of articles by Mr. Schmeck and congratulates both the writer and the newspaper upon the accuracy and general reportorial excellence they represent.

THE CLINICAL CENTER of the National Institutes of Health, where—under one roof—both basic and clinical research are joined with patient care in a continuing study of the world's health problems.

NIH—"Capital" of U.S. Medical Research

By HAROLD M. SCHMECK, Jr.

ONE of the nerve centers of a growing revolution in biological science is housed on 305 rolling acres northwest of the nation's capital.

Here, bursting the seams of forty buildings on a "campus" near Bethesda, Md., are the National Institutes of Health, the main research establishment of the United States Public Health Service.

Here are more than 2,500 scientists and research workers studying the whole nature of man, of some of his friends and most of his enemies on this planet. There are studies, slated to take years, assessing the way ordinary people grow old; studies focussed on a single very special chemical and its metabolic pathways through the body; searches for new weapons against disease and for new tools to prize open some of life's most crucial puzzles.

In the establishment are seven institutes: The National Cancer Institute; National Heart Institute; National Institute of Allergy and Infectious Diseases; National Institute of Arthritis and Metabolic Diseases; National Institute of Dental Research; National Institute of Mental Health; National Institute of Neurological Diseases and Blindness.

There are also four divisions: Biologics Standards, General Medical Sciences, Research Grants, and Research Services.

An ultra-modern 500-bed hospital called the Clinical Center crowns the institutes' facilities.

Here are patients afflicted with some of man's most bizarre diseases and other patients who are not suffering from any ailment at all. The latter, all volunteers, often serve as normal "controls" so that scientists can study, for example, the difference in response to a given situation between the normal and the person afflicted with a specific disease.

THE institutes, as Dr. G. Burroughs Mider, director of laboratories and clinics, points out, are dedicated to the idea that the future of medicine lies in scientifically oriented research.

It is in such research, running the whole gamut of biology on earth and probing ever deeper into the most minute and detailed processes of life, that many scientists see burgeoning a fresh revolution momentous for mankind.

"We are all convinced that the impact of science on everyday affairs is just really beginning to be felt," said Dr. James A. Shannon, director of the institutes in a recent interview in Bethesda.

Not long ago one of the nation's brilliant theoretical physicists predicted that biology's accomplishments in the next fifty years might dwarf even the explosive impact of physics in the last fifty.

Obviously, the National Institutes of Health claim no authorship of this revolution, which rests on the immense base of work in the life sciences throughout the world. The institutes and their research, however, are typical of it and in many ways are helping shape its course.

The institutes are an integral part of the American scientific community. They influence it through their own scientists' work and are in turn influenced by it. They aid the community through widespread research grants that make up a substantial part of the income of the many medical schools and university departments whose research the institutes help support.

THE institutes also have a special role to play in operating large research-development programs whose scope would be beyond the capabilities of any private institution.

Perhaps the best known of these is the huge drug-screening program of the Cancer Chemotherapy National Service Center. More than 135,000 compounds have been screened for anticancer activity since the program began five and a half years ago. By now 160 of the most promising anticancer agents have been, or are now being, used experimentally in treating patients at hospitals throughout the United States and in

INSIDE THE CLINICAL CENTER are more than 1,000 laboratories, in addition to rooms for more than 500 patients. Many more laboratories are scattered throughout the 42 buildings which make up the NIH complex. Pictured here is a scientist in a biochemical laboratory.

Research workers on 305-acre "campus" are studying the whole nature of man, some of his friends, and most of his enemies at this burgeoning establishment in a Washington, D.C. suburban area.

parts of Western Europe.

The Administration's budget for the fiscal year 1962 calls for $623,300,000 to operate the National Institutes of Health and their programs. This is not a figure to bring a gasp from men hardened to the dollars-and-cents realities of space and defense research, but it represents a huge sum to medicine and biology. Soon Dr. Shannon and other officers of the institutes will go before Congress to explain in detail what is to be done with these funds.

The institutes' expenditures for research and research training have grown by more than a third in each of the last two years and they now comprise a sum five times as great as it was five years ago. Nevertheless, medical-research spending remains only about 5 per cent of the nation's total research budget.

Despite the importance of other commitments, the institutes "continue to be primarily a research institution of acknowledged excellence, imagination and drive," Dr. Shannon points out.

THEIR scientists can be credited with many recent accomplishments of importance.

Less than a year ago, for example, specialists of the National Institute of Allergy and Infectious Diseases made the chance discovery that monkey malaria could be transmitted naturally to man. The finding is being followed up urgently because it could conceivably raise questions affecting the whole world-wide program to stamp out this disease.

Scientists at the National Institute of Dental Research have found strong proof that tooth decay is an infectious disease and that, for any given species of living creature, there may be one germ alone that causes it. This too is being hotly pursued at the institute and elsewhere because the concept could prove immensely important to every man and woman who has a tooth.

Typical of the great current interest in biology "at the molecular level" is a study recently completed at the Institute of Arthritis and Metabolic Diseases. It is considered of potentially great significance, throwing light on the chemistry by which basic life processes proceed.

Fundamental to all such processes are enzymes. These are proteins each tailored for one very specific biochemical task such as the chemical degradation of one particular substance.

Research by Dr. Gordon M. Tompkins and Dr. K. Lemone Yielding showed that a hormone could break such an enzyme into four fragments and, by doing so, would destroy the enzyme's activity against one substance and make it active against another.

THE principal reacting substances studied were stilbesterol, a synthetic steroid that has properties like those of natural female hormones, and the enzyme glumatic dehydrogenase. The enzyme's normal chemical function is to break down glutamic acid, one of the basic building blocks of protein. In the presence of stilbesterol, however, the enzyme is broken into four fragments, inactive against glutamic acid but active against another building block of protein called alanine.

This is believed to be the first clear demonstration of the way in which a pure hormone and a pure enzyme react to achieve the body's complex needs. Although the profound influence of hormones on enzyme action has been long appreciated, it has previously been little understood. Specialists at the institute believe the research may influence greatly the direction of future study in this area of basic biology.

At the Institute of Neurological Diseases and Blindness scientists have identified specific chemical disturbances in a rare and baffling disorder called familial periodic paralysis. Victims of this hereditary ailment are subject to rapidly developing attacks of muscular weakness so severe as to render the victim helpless. The attacks of flaccid paralysis usually occur at night and commonly last less than an hour. Some attacks, however, may persist as long as two days.

The quest for an explanation of these

AGGRESSIVE RHESUS MONKEY, "King," who once ruled a colony of simians at NIH, is an example of the type of monkey vital to research and testing, especially in connection with polio vaccines.

TOLEDO SCALE COMPANY, TOLEDO, OH
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NO SPRINGS HONEST WEIGHT

"HOW MUCH DO I WEIGH?" This white rat seems to be curious about his avoirdupois, and rightly so, for he is a member of a nutrition research team, one of many thousands of his kind employed in research studies at NIH.

NIH—Capital of U.S. Medical Research

episodes involved many scientific approaches in research by Dr. G. Milton Shy, the institute's director of clinical research, and Theodor Wanko, Peter T. Rowley and Andrew G. Engel, his colleagues.

THE work disclosed that an excess of water invaded individual muscle cells in these attacks and probably hampered the cells' function. In certain of the cells, it was further learned, there is an accumulation of substances that must stem from a basic fault in the body's use and handling of sugar.

The disease is rare and fortunately claims few victims, but its scientific interest is greater than the number of patients might suggest. Like other diseases probably based on inborn metabolic faults, this disorder offers the research scientist valuable insights into the most intimate functioning of the body and on the huge derangements that seemingly minor biochemical changes can produce.

Today the so-called metabolic or molecular diseases constitute one of medical science's most vigorously challenged frontiers.

The total research endeavors of such a huge enterprise involve scientific logistics on a mammoth scale.

FOR its scientists the institutes breed and issue in a year's time 800,000 mice and 300,000 rats, many of them of special inbred strains. Also produced are 200,000 other small animals such as hamsters, guinea pigs and rabbits.

Most of the large animals employed in research are bred elsewhere and procured through commercial channels. The census last year was 2,300 monkeys (the number will be doubled during the coming fiscal year), 3,500 dogs, 3,000 cats and small numbers of various other animals. One research project last year even asked for, and received, a few seagulls.

Culture media, used for growing bacteria and other organisms, also is a large-scale matter. The unit responsible for this vital, though unglamorous, necessity of research supplied 11,360 gallons last year, although the needs of any individual experiment are unlikely to total only a few hundredths of an ounce.

This catalogue of large numbers reflects a scientific enterprise of extraordinary depth and breadth. Summaries of the research results for just a single year occupy a full yard of shelf space in the office of Dr. Mider.

"We probably embrace a larger segment of biomedical research than any other organization," Dr. Mider observed.

MORE THAN 800,000 MICE such as these are bred and issued to scientists at NIH each year for use in research studies. These particular mice represent strains which have been inbred for many years in studies of heredity.

Cancer Institute Spurs Virus Search

Although viruses are known to cause a number of types of cancer in animals, clear proof of a cause-and-effect relationship in man still is lacking. Large new research program was launched to find the facts.

By HAROLD M. SCHMECK, Jr.

A MULTITUDE of viruses, real and imagined, haunt modern cancer research like tiny malignant ghosts.

Viruses are known to cause a number of different cancers in animals. If they can be incriminated as an important cause of human cancers, too, the proof will be a strong lever with which this murderous group of diseases may some day be toppled.

But although finding viruses is becoming almost easy, proving their guilt in human cancer is incredibly difficult.

In recent months there have been many provocative reports, but most of these have been challenged and clear proof of a cause-and-effect relationship between any human cancer and any virus is still lacking.

So high are the stakes, however, and so intense the interest among scientists that the National Cancer Institute has begun a multi-million-dollar assault on the whole virus-cancer problem.

Planned with the guidance of the National Advisory Cancer Council and other experts, this assault includes stepped-up support for independent research, large-scale programs to provide new tools for the job and several lines of independent research at the institute itself.

SOME of the problems are formidable. Viruses can be present, but not guilty; could be guilty, but not detectably present. Experiments can activate latent viruses thus adding fresh complication to an already abundantly complicated problem.

There are so many viruses already known that the matching of a presumed new one against all those already identified is a huge, expensive task.

Viruses are parasites that must have living cells in which to grow and multiply. Whether these cells are in laboratory tissue culture or in living animals, they are usually contaminated with viruses known and unknown. A scientist's problems can multiply as fast as his viruses unless he knows exactly what contaminants are present before trying to grow something new from cell-free extracts of cancer tissue.

"The individual scientist is hard put to it to solve all these problems," said Dr. Kenneth M. Endicott, director of the National Cancer Institute, during a recent interview in Bethesda, Md. A major task in which the institute's programs can help, he indicated, is in forging the needed basic tools.

One vital need is for establishing standard dependable lines of cells of known purity in which viruses can be grown in the laboratory. In the profusion and quantity needed these are simply not available. Last year a Cell Culture Collection Committee was set up to overcome this important research deficit.

A cooperative program has been started to establish such certified cell lines and to preserve samples of "seed stocks" in special liquid nitrogen refrigerators. In these, the cells will be held in a sort of inanimate immortality at a temperature more than 300 degrees Fahrenheit below the freezing point of water.

AT this temperature, said Dr. Harvey I. Scudder, chief of the institute's viruses and cancer program, the stocks should be safe from molestation by anything but cosmic rays.

A comparable program has been set up to provide the biochemical tools needed by many scientists for routine identification of viruses. The first phases of this will produce standard typing reagents for roughly ninety human viruses, according to Dr. Scudder. A first contract in the program was let last year to a University of Kansas group.

The immensity of the task scientists face in grappling with viruses on a large scale can be judged from the fact that roughly 400 viruses of man and other animal species have already been identified. No one believes all have been found.

If there really are human cancer viruses it may well be that they are among those already discovered and thought to be "harmless." They may also be still undiscovered. It may be that a normally inoffensive virus occasionally runs amok for obscure reasons.

There is also considerable evidence, as Dr. C. Gordon Zubrod, the institute's director of intramural research, points out, that cancers may stem from "cooperative causes"—a virus with some other agent, for example.

If this were not complicated enough, there is evidence from animals that some cancers may stem from viruses taken in by the newborn infant, producing the disease only years later, after all tangible sign of virus has vanished.

Just as standard tissue culture lines are vital, so are standard animal "hosts" in which to grow the tiny particles.

Another major program being advanced by the institute, therefore, is one to establish lines of animals bred either free of viruses or harboring only ones that are known.

The interest in animal studies goes beyond the traditional mice and rats to

(*Continued on page 15*)

TECHNICIANS IN CANCER RESEARCH laboratory check test tubes containing virus cultures.

STUDIES OF AGING SPAN THE YEARS from cradle to the grave. Psychologist here tests child's motor development.

Scientists Push Studies of Aging

By HAROLD M. SCHMECK, Jr.

A FULL portrait of the seven ages of man is being drawn with the help of the National Institutes of Health.

The picture will cover far more territory than Shakespeare's immortal thumbnail sketch of man's progress from infancy to old age. It will be a detailed medical chronicle beginning months before birth and ending with death.

The research seeks to answer such questions as how and why people grow old; what events affecting an expectant mother also affect her unborn child and how creative people make the crucial transition from adolescence to adulthood.

Scientists everywhere, of course, are contributing as they probe many aspects of human experience between the two mortal events of conception and death. Some parts of the picture, however, require a huge effort beyond the scope of any single research center. In coordinating such major efforts as well as in [illegible] "intramural" research programs, the institutes help paint the total picture.

A PRIME example is the collaborative perinatal study directed by the National Institute of Neurological Diseases and Blindness. Its central office is the institute's perinatal research branch, of which Dr. Heinz Berendes is chief.

It is estimated that three American babies in every 100 born have some degree of mental retardation; that one in sixteen suffers from some disorder of nervous system, sight or hearing. It is estimated that one pregnancy in five fails to produce a living child.

The cost of this in human waste and heartbreak is enormous. The stake of science in finding out why the tragedies occur and how they can be prevented is correspondingly great.

The perinatal study is enlisting 50,000 expectant mothers to find the answers. It is probably the largest study of its kind ever attempted.

The project is a prospective study. It doesn't start with the handicapped child and work backward to find out where the accident occurred. Rather it starts with a large number of mothers-to-be, observes them closely throughout pregnancy and matches the mother's experience with the "outcome" expressed in the normalcy, or departure from it, of her child.

It is well known, for instance, that German measles, infecting a woman early in her pregnancy, can endanger the unborn baby.

DO other infections carry a risk? Could use of certain drugs be harmful? What is the effect, if any, of a severe emotional shock? Why does it seem that parents in the lower socio-economic groups are more likely than others to have a premature baby?

Clear answers to questions such as these are almost impossible to get if the search starts only after a child is born and an abnormality has been discovered.

To produce statistically significant results, even in a prospective study, a sample of 40,000 babies is needed, according to Dr. Milo D. Leavitt, assistant director of the institute's perinatal research section.

To insure getting at least that many babies, 50,000 mothers-to-be are being enrolled by fifteen of the nation's important teaching medical centers. The recruiting started two years ago and the enrollment now stands at about 13,500 mothers and more than 8,000 babies. The project is to expand at the rate of 9,000 mothers a year.

The centers have also collected some 260 brains of stillborn babies and those who died soon after birth. At the institute in Bethesda, Md., a special laboratory is being set up to study these brains.

Eventually each mother in the study will be represented by a sheaf of data and by sixteen highly important little bottles, each containing blood serum. Just begun, with the cooperation of the Institute of Allergy and Infectious Diseases, is a search through the blood samples for telltale antibodies.

This should reveal what infections the mother had during the whole course

VOLUNTEER PATIENT IN AGING STUDY, a member of the Select Society of Seeking Scientists, Saints and Sinners, tests muscle strength on hand dynameter.

Seek answers to questions concerning how and why people grow old, from prenatal period through adolescence to old age.

of her pregnancy, even though some of these will have been so slight as to have passed unnoticed at the time.

The samples will also be studied for other clues, such as the state of the mother's thyroid function. Part of each sample will simply be kept on file in cold storage. It may be that tests and relationships still undiscovered can be brought to bear on the research years from now.

In a study as big as this, "results" are not to be looked for soon. So far the scientists helping guide the project will say only that some hints and suggestions, not yet possible to evaluate, have cropped up.

Among these is the finding that cerebral palsy appears in about one per cent of one-year-old children in the study, whereas previous estimates of its frequency have ranged from a half to nine-tenths of one per cent.

Six or seven years of further work will probably be needed to produce final results, Dr. Leavitt said. When they do become available, these may well show ways of cutting sharply the present toll in handicapped and stillborn infants.

The great majority of the 40,000 children, of course, will be born without defects, will grow up and grow old. This latter process—and scientists are not yet sure just what it is—makes up another important part of the human life portrait that science is painting.

A MAJOR center for this wide-ranging research on aging is the gerontology branch of the National Heart Institute, housed at the Baltimore City Hospital, in Baltimore, Md., and headed by Dr. Nathan W. Shock.

While other scientists are waiting for children to be born, Dr. Shock is watching today's adults grow old. He does this with a group, called the "Six S's," which probably has no close counterpart anywhere.

The full name is the Select Society of Seeking Scientists, Saints and Sinners. The membership, about 300 men, ranges from Baltimore youths in their late teens to a 100-year-old emeritus professor at Cornell University in Ithaca.

Every eighteen months each member spends two crowded days in Dr. Shock's laboratories undergoing all kinds of tests, biochemical, physical, neurological and mental. The men have volunteered to keep these periodic rendezvous with science as long as they live.

Most of the published data on aging, Dr. Shock points out, has always been gathered from the sick, the hospitalized and those in other institutions.

The big question, whether there is a generalized aging process and, if so, how it works, cannot be answered by concentration on sick persons alone.

Statistics seem to indicate that tangible signs of aging begin at about the age of thirty and mount gradually for the rest of a person's life, but Dr. Shock said he was not sure this was a true picture. Several alternatives are possible in the light of what evidence exists. Some of the major organs, the kidneys, for instance, seem to "age" more rapidly than the body as a whole.

One of the eternally baffling questions of growing old is why one person will seem to surrender while another fights his disabilities to a standstill until the day of his death.

"We see people coming in here," Dr. Shock said, "who are holding down responsible jobs and yet actually have as much disease in them as other people who are in hospitals. I want to know why some people simply give up and throw in the sponge while others just grit their teeth and keep on going."

Though the Six S's research is by no means the largest part of the branch's work, nor even its only project working with an outside population, Dr. Shock considers it one of the most important.

The project will be working some of the Six S volunteers into their third round of tests this summer, but to bear fruit the project must continue much longer.

"I can't answer any of the questions I want to answer in less than ten years," Dr. Shock said.

Of course not all progress in understanding aging is tied to such long-range studies. An institute scientist who has since joined the faculty of the University of Virginia, in Charlotte, recently found one interesting clue in a laboratory study of cockroaches.

It has been known that a young cock-

(*Continued on page 8*)

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Scientists Push Studies of Aging

(*Continued from page 7*)

roach who loses a leg will promptly grow a replacement, a feat of which older members of the same species seem incapable.

By surgery, Dr. Dietrich H. Bodenstein connected pairs of cockroaches, one young the other old, to make them artificial Siamese twins. When linked to a young specimen the older actually regained its ability to regrow lost limbs.

This hints strongly that there is something tangible in a creature's internal environment that plays an important role in the aging process, Dr. Shock said.

ANOTHER hint came through the study of mitochondria, the tiny bodies, either spherical or rod shaped, that serve as the powerhouse of living cells. Dr. D. Rao Sanadi has found that the mitochondria in a rat liver cell have a half life of only about ten days. In other words half of any group of them will survive only that long.

Great possible significance is attached to this. It shows that a cell's genetic machinery must be capable of forming as complex a structure as a mitochondrion not just once, but repeatedly. Loss of the ability to direct such a complex fabrication job would fatally deprive a cell of its sources of useful energy.

Important as they are, neither aging nor the physiological perils of earliest life make up the whole human panorama. Filling in still other parts are a number of studies at the National Institute of Mental Health.

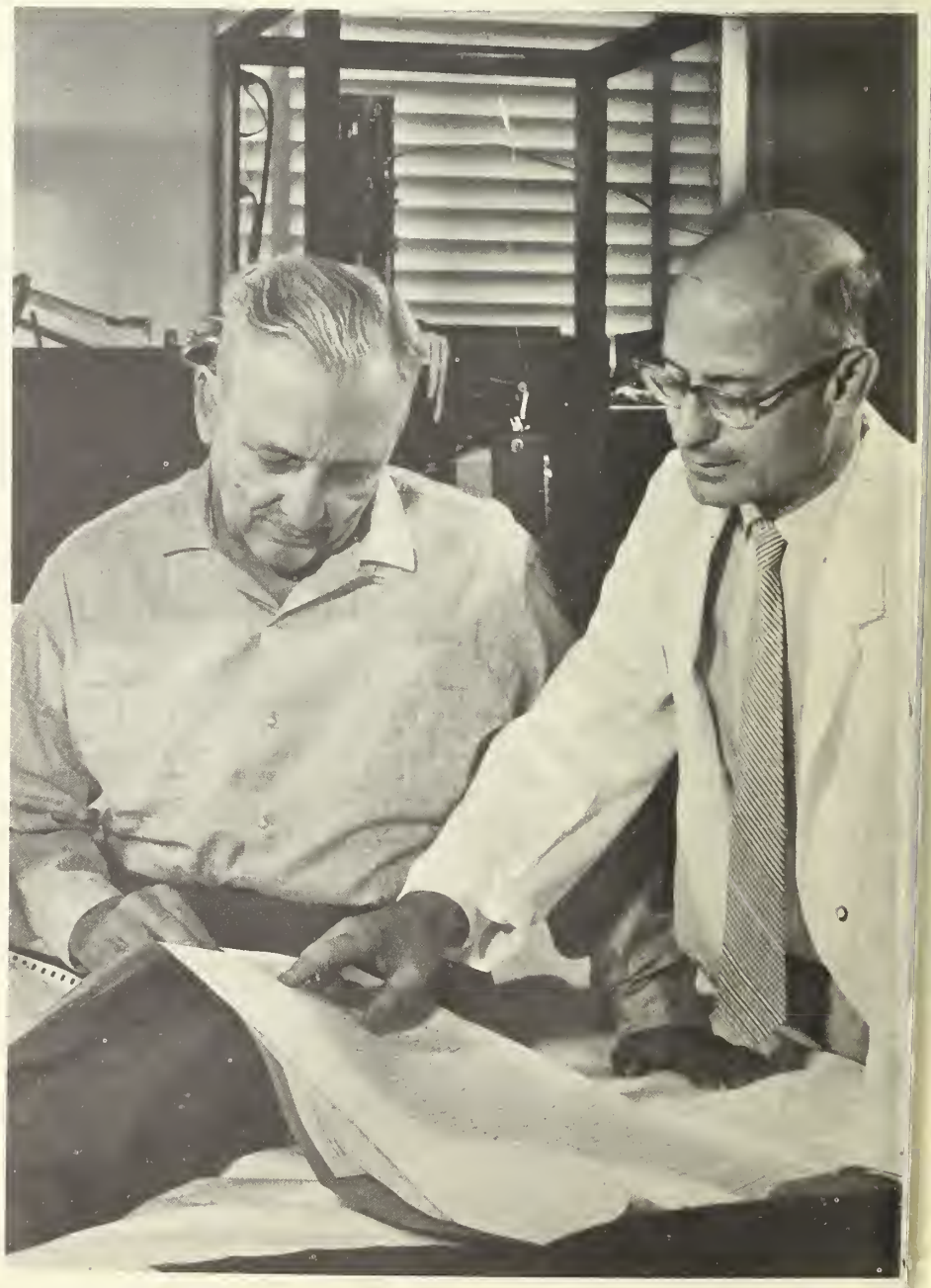
One group has recently studied the manner in which capable high school seniors cope successfully with the transition from high school to college.

In many ways this step represents the change from adolescence to adulthood, according to Dr. George V. Coelho and Dr. Earle Silber, two of the principal authors of the study.

To discover how resourceful youngsters manage this change, the scientists went to a group of seniors in a near-by Maryland high school, interviewed them repeatedly in depth, talked to their families and then continued the process during the students' freshman year in college.

SMALL MUSCLES IN HAND of aging study volunteer are stimulated by an electrical shock in this test.

MUSCULAR DEVELOPMENT of infant is noted by doctor who checks ability of child to raise head at age of four months.



"SIX S" MEMBER CONFERS with head of gerontology project on results of tests.

A HAPPY MOTHER and her newborn child open a new chapter in life's story—at the beginning of human development and the aging process.

Rabbits Medical

The droop-eared rabbits pictured experimental animals who contribu every day in the year.

These particular rabbits cooperat knowledge concerning the action ar drugs, such as cortisone, hydricortis treatment of rheumatic diseases, pa

The young rabbits used in this stu extracted from the papaya plant. as a meat tenderizer, causes basic when it is injected. These changes erect ears. (Users of papain meat effects, however, for the enzyme is de cartilage restoration takes place qu ears recovering their usual tone an found, however, that the ears woul cartilage recovery—if daily injectio injections were discontinued the ea

BUNNIES IN BOXES, waiting to h e th

Left, above
BEFORE HIS SHOT of papain, ears erect . .

Left, below
AFTER INJECTION, early effects, on ear down . . .

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traits made.

Right, above
A LITTLE LATER, both ears at half-mast . . .

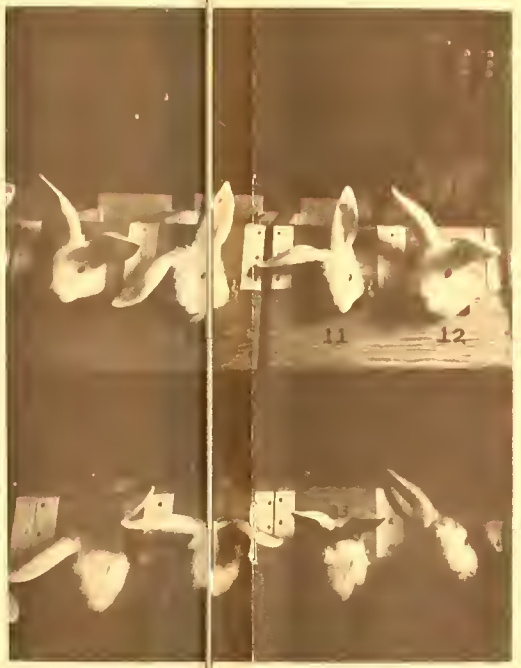
Right, below
FINALLY, the hound-dog look, ears dragging. But, in a day or so, they'll be back to normal and he'll feel natural again.

Rabbits Aid Medical Research

The droop-eared rabbits pict ed on this page are representative of the many experimental animals who cont ibute to the advancement of medical knowledge every day in the year.

These particular rabbits coope ated with scientists in studies which produced new knowledge concerning the actio and effects of steroid drugs on cartilage. Steroid drugs, such as cortisone, hydric tisone, and prednisolone, are widely used in the treatment of rheumatic diseases, particularly rheumatoid arthritis.

The young rabbits used in this tudy were given injections of papain, an enzyme extracted from the papaya plant. Papain, commonly used in homes and restaurants as a meat tenderizer, causes ba c changes to occur in the rabbit's body cartilage when it is injected. These chang s result in the progressive collapse of their normally erect ears. (Users of papain m at tenderizers need not be concerned about such effects, however, for the enzyme is deactivated by heat used in cooking.) Ordinarily, cartilage restoration takes place quickly after injections of the enzyme, the rabbits' ears recovering their usual tone and erect state within three to five days. It was found, however, that the ears w ld remain collapsed—indicating interference with cartilage recovery—if daily injec ons of steroid drugs were given. When the steroid injections were discontinued the ars became erect again.



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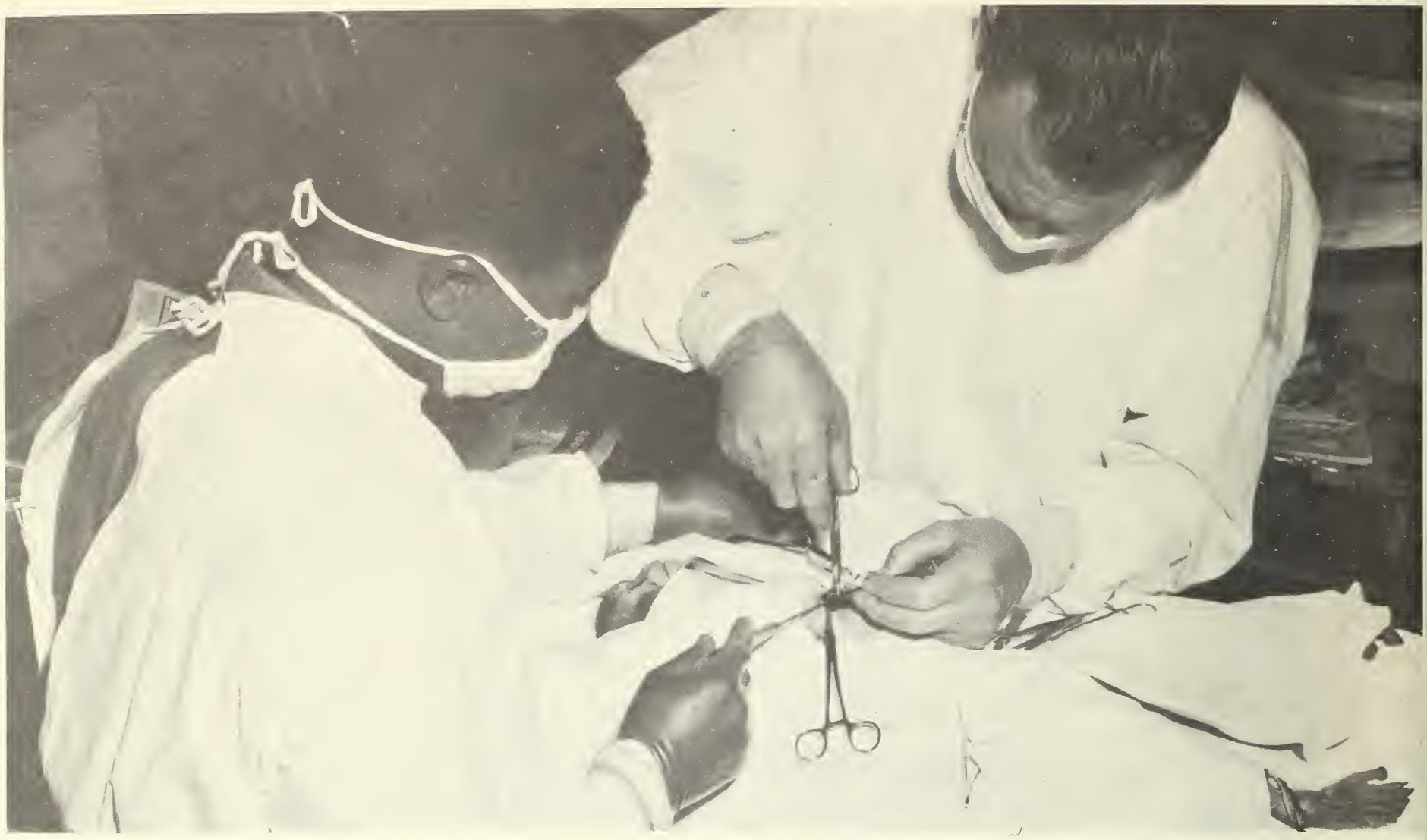


SCIENTISTS IN NIH LABORATORY perform surgical operation on monkey in course of research project on malaria.

Advances Made in Malaria and Virus Studies

Investigators find monkey malaria is transmissible to man via the mosquito. They also search for more of the many viruses which cause colds, flu and other respiratory illnesses.

By HAROLD M. SCHMECK, Jr.

ABOUT a year ago two scientists in Memphis caught malaria.

There was little question as to where they contracted the disease. The scientists were staff members of a research laboratory operated by the National Institute of Allergy and Infectious Diseases. They were studying malaria, handling and dissecting thousands of infected mosquitos.

The surprising thing about the incident was that the malaria involved was of a type known to infect monkeys, but previously believed harmless to man.

The unexpected illness initiated a whole series of investigations during which it was proved conclusively that two types of simian malaria could be transmitted from monkey-to-mosquito-to-man and vice versa.

This finding, which challenged a view almost universally held by the world's malaria speicalists, was first reported by Dr. Don E. Eyles, Dr. Robert Coatney and Dr. Morton E. Getz of the institute. The viewpoint thrown into question was that, in nature, cross-infection between monkey and man would be so rare, if it happened at all, unimportant.

Ordinarily malaria is transmitted from one person to another by the Anopheles mosquito. The mosquito becomes infected with the malarial parasite when it sucks the blood of an infected person. It later transmits parasites to fresh victims in the course of biting them.

MALARIA probably still afflicts more than 100,000,000 of the world's population and it may kill more than 1,000,000 yearly.

If monkeys must be considered possible reservoirs of infections that can later be transmitted to man, the problem of malaria eradication in some regions might be greatly complicated.

Both of the strains of malaria involved in the recent human cases came originally from Malaya, Dr. Justin M. Andrews, director of the institute, said during a recent interview in Bethesda, Md.

Periodically malaria specialists have wondered whether animal malarias could be transmitted to man, Dr. Andrews said, and occasionally there was some evidence pointing in this direction. In the laboratory, however, intentional cross-infections had usually been unsuccessful. Those that succeeded were achieved with great difficulty.

The new work gives an interesting sidelight on this.

IN the monkey malaria strains it was found that the incubation period following the first transmission from mosquito-to-man was unusually long. With repeated infections in man, however, the monkey malaria parasite apparently became better adapted to human blood and the incubation period dropped sharply.

The new discovery concerning monkey malaria could prove to be only an interesting laboratory curiosity. On the other hand, it could be a matter of considerable public health importance.

The real question, of course, is how these malarial strains act in nature. To study the problem in its natural setting the institute is now setting up a field research unit near Kuala Lumpur, Malaya, Dr. Andrews said.

He emphasized that the extent of present knowledge gave no cause for alarm over the prospects for malaria eradication even in regions where monkeys were numerous.

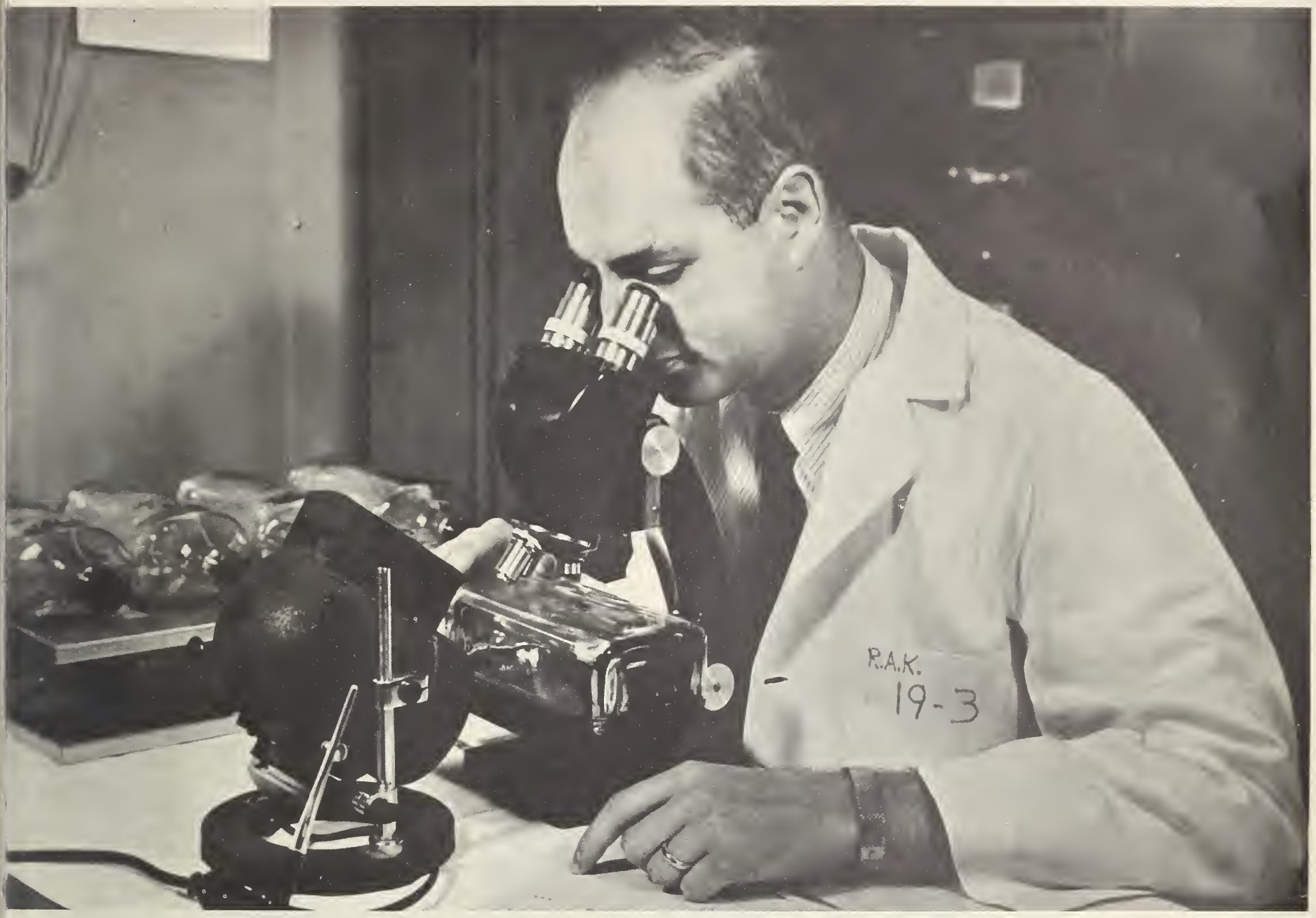
Paradoxically there is one respect in which the two monkey malaria strains are almost sure to be of value to medicine. They provide for the first time means of testing new anti-malarial drugs in monkeys against forms of the disease common to the monkey and to his distant relative, man.

The original incident and its still-incomplete aftermath serve to illustrate this fact: microbiology, always a foundation stone of medical science, is still an area with frontiers in which surprises are to be encountered.

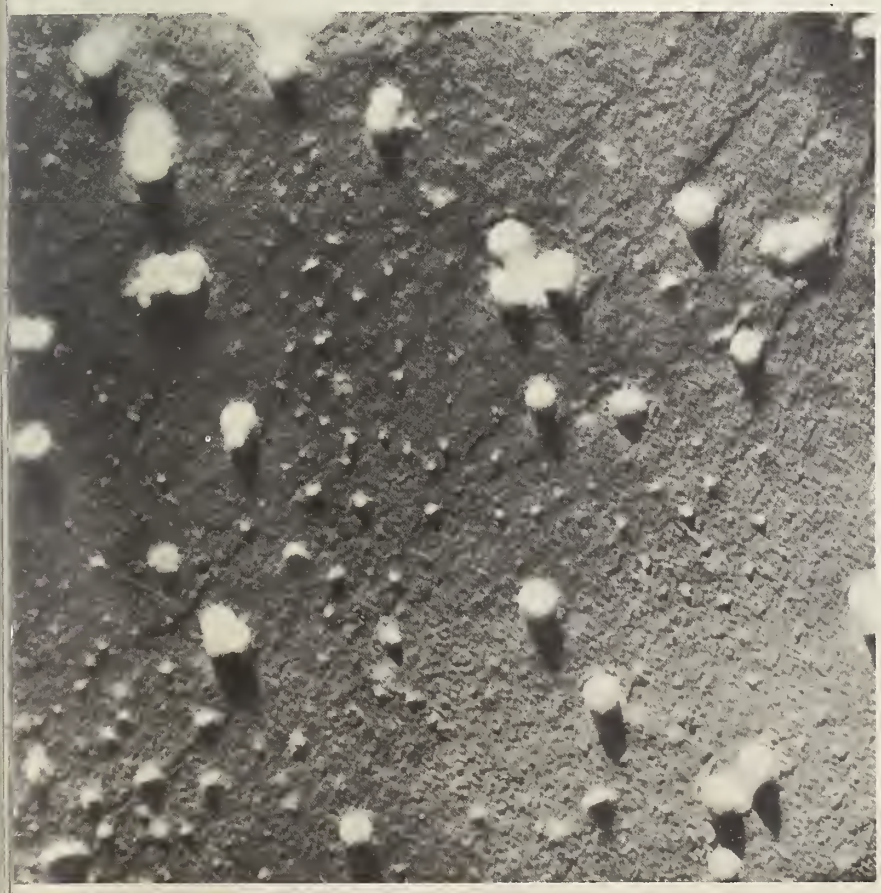
Another vital frontier in this branch of biomedical research concerns study of those viruses that produce illness of the human respiratory tract—colds, influenza and some types of pneumonia. In terms of sheer numbers of people and bouts of illness involved, these viruses rank first among the known causes of illness of mankind.

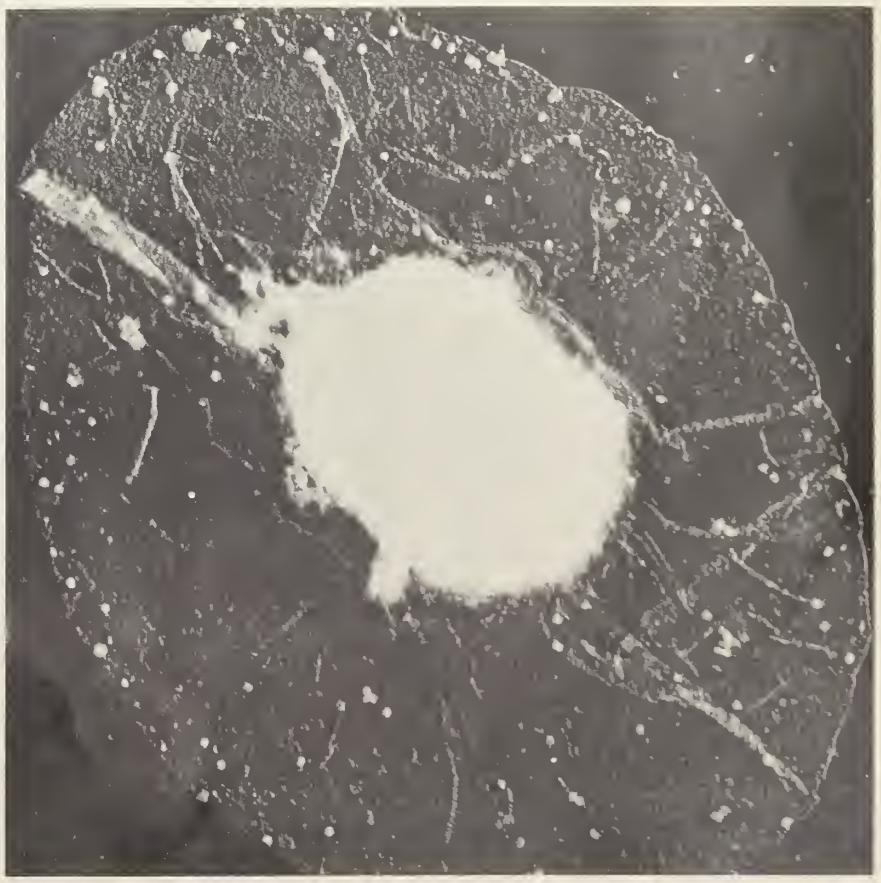
No one has ever chronicled completely the natural ebb and flow of viruses through a large group of people, but studies at the institute are aiming in this direction. They show that for known viruses in a closed population, such as an orphanage, the events can be traced with great accuracy.

(*Continued on page 14*)



NVESTIGATOR (above) examines a virus-infected tissue culture. UNDER THE ELECTRON microscope (below, left) influenza viruses appear as small woolly spots in a chicken blood cell. A MORE DETAILED STUDY of virus particles (below, right) as they appear through the electron microscope. *Note:* Microscope used by scientist in photo at top of page is an ordinary optical microscope. See photo of electron microscope on page 15.





Malaria and Virus Studies

(*Continued from page 13*)

"You can tell the day a virus enters and the day it goes," Dr. Andrews said.

Yet, in many cases, the person with whom the virus visits is quite unaware he has taken in a temporary squatter.

Man's knowledge of these capricious agents has accumulated rapidly in recent years, according to Dr. Dorland J. Davis, associate director for research of the institute.

FROM 1933 to 1953 only about 5 per cent of serious illnesses of the respiratory tract could be matched with a specific known virus, he said. By a year ago the figure had risen to about 35 per cent. Today, the scientist estimates, fully 60 per cent of those virus respiratory illnesses of children serious enough to put the patient in a hospital can be matched with known viruses. The figure is somewhat lower for adults.

Involved are some twenty to thirty viruses. Presumably others remain unknown and yet to be discovered and some may be only hitch-hikers having no active role in disease.

If the guilty virus can be captured, vaccines can probably be produced to protect against them.

"The hooker is that until knowledge of the viruses is complete there is always the possibility of leaving out one which is vital," Dr. Andrews remarked.

Another crucial question is whether or not really large numbers of viruses can be combined into a single effective vaccine.

The institute's plans call for research in the next five years to answer that important question.

Two of the clearly important infectious agents linked to human pneumonias during the last year are the Eaton agent and a group of viruses called syncytial viruses.

Experience with the Eaton agent shows that all progress against the atypical, or virus, pneumonias need not necessarily wait for the development of protective vaccines.

THE agent is an abnormally large virus or virus-like particle discovered seventeen years ago. Its discoverer, Dr. Monroe Davis Eaton of Harvard, believed it to be among the causes of pneumonia, but his evidence was seriously disputed by other virus specialists.

Recently Dr. Robert M. Channock and his colleagues at the institute and elsewhere established beyond much doubt that the Eaton agent was an important cause of pneumonia.

A study done in collaboration with Children's Hospital in Washington showed that 10 per cent of all infants and children hospitalized with pneumonia were infected with Eaton agent.

Another study, done cooperatively with Navy medical officers, showed the Eaton agent present in over half the pneumonias occurring during a year's time at the Marine Corps training center, Parris Island, S.C.

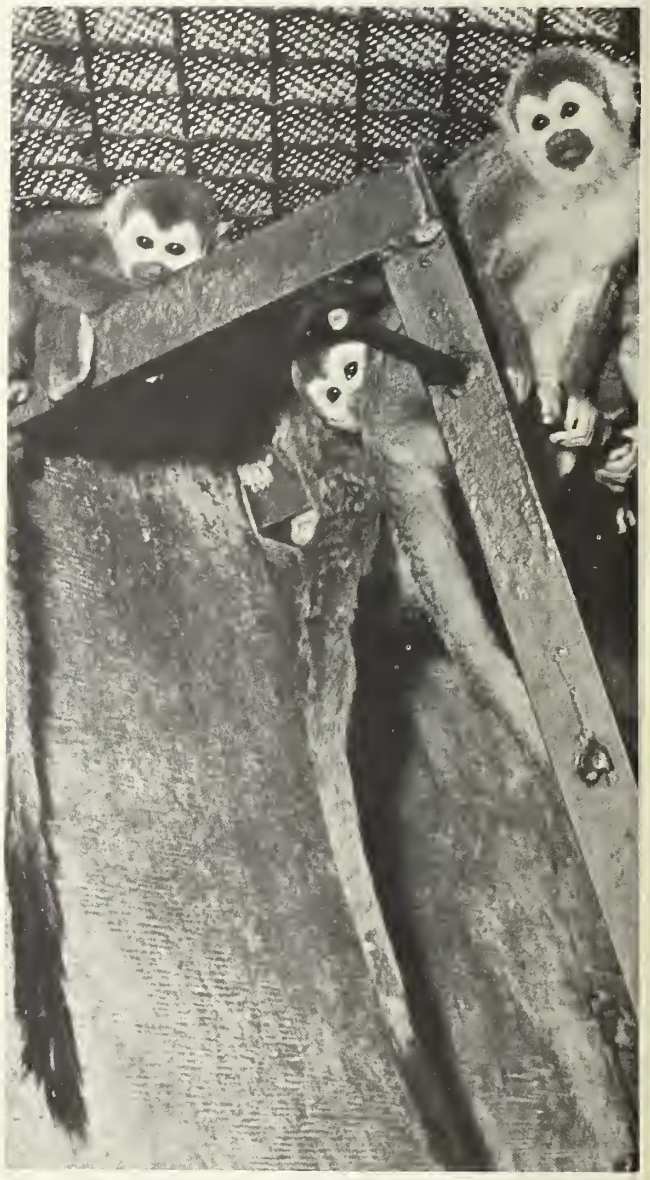
More recently the researchers have found that certain antibiotics—the tetracyclines—are effective against Eaton-agent pneumonia, although virus infections are ordinarily impervious to drugs.

The institute's investigations of microbes make up only a part of its work, but they touch on a broad range of human miseries in this country and abroad. The range includes parasite diseases that afflict Asia and Africa, the viruses that cause the common cold and the other viruses responsible for deadly attacks of encephalitis.

Altogether the work forms a part of the giant effort of medical science everywhere to expunge the ancient terror that has always clung to words such as contagion.

MOSQUITOES AND OTHER BLOOD-FEEDING insects in plastic cages are fed on blood from laboratory worker's arm. The insects are employed in studies of insect borne diseases.

LABORATORY WORKERS DISSECT MOSQUITOES in connection with studies of simian malaria and its transmissibility to man.



SQUIRREL MONKEYS IN NIH ANIMAL quarters stare bashfully at camera. Note extremely long, muscular tails.

Cancer Institute Spurs Virus Search

(*Continued from page 5*)

monkeys and other primates, because the need is seen to try out "hot suspects" among the viruses in animal species closely related to man.

If a large-scale search for viruses in human cancer is indeed to be made, samples of human tissue, cancerous and non-cancerous, must be made widely available. This, too, is being explored because, although more than 250,000 Americans may die of cancer each year, suitable tissue specimens in which to search are in short supply.

The collection of such tissue samples requires standards of purity and freshness considerably more exacting than even the normal requirements of surgery and pathology.

Several research projects at the institute itself illustrate the ways in which such tissue samples can be important in the hunt for fugitive viruses that may possibly be related to cancer.

One project, considered highly exciting by specialists at the institute, employs the electron microscope, an instrument so powerful in magnification that it can show the shadow cast by a single virus particle. So far in this research five kinds of animal leukemia have been studied.

In each case Dr. Albert J. Dalton has found characteristic structures, appearing like double rings, in certain bone marrow cells called megakaryocytes. Among specialists there is little doubt that these structures are virus particles. They are of uniform size and are not to be found in the cells of normal animals. The five animal leukemias in which these particles are found are all known to be caused by viruses.

AMONG human cancers it is leukemia that is most actively suspected of being caused by virus. Dr. Dalton has just begun a search of human bone marrow cells to see if the telltale structures present in five animal leukemias may also be present in human leukemia. If he finds them, this would be impressive proof indeed.

The institute's search for viruses in human cancer is really made up of several independent projects, according to Dr. W. Ray Bryan, chief of the section in which this work is done. There is, however, a grand strategy that involves putting the suspected human tissue material to a wide variety of tests.

For most of these the basic raw material is a human tissue sample, treated chemically and spun in a centrifuge to concentrate the portion in which virus might logically be found.

The little solid pellets of concentrated material then go through a battery of tests.

One pellet may be split in half and a lengthwise slice studied under the electron microscope. The search through a single pellet for traces that might be virus takes a full day.

In another study the material will be inoculated into five different tissue cultures. Later cell-free material from these cultures will be reinoculated into new cultures and the process repeated again. Still later, material will be inoculated into newborn mice and a portion frozen and stored. A search is also made by electron microscope for virus-like particles.

OTHER scientists will try to grow their suspected material in chicken eggs or, to economize on space, Japanese quail eggs, which are much smaller.

Others are inoculating the pellet material directly into newborn mice. A major effort, now being planned, is to inoculate the suspected material in newborn monkeys.

One of the basic problems is that some viruses capable of inducing a cancer in one species of animal will not do so in others. Therefore it is quite possible that a real human cancer virus would simply not produce cancers in mice, rats and other common laboratory animals.

One highly promising way around this predicament is being pursued both at the institute and in laboratories elsewhere.

Viruses are known to be packets of nucleic acid encased in protein coats. It is evidently the nucleic acid that is infectious while the characteristics of the protein coat determine what cells and species will be infected.

There are chemical means of freeing nucleic acid intact from viruses that might be present in a sample. Attempts are being made to produce cancers in newborn mice with such "naked" nucleic acid. It is hoped that a cancer virus can be made, in this way, to jump species lines and cause cancers in animals that would ordinarily be free from attack by the whole virus. There is recent evidence from animal cancer viruses that such species jumps can be achieved.

The research war against cancer is being fought in laboratories everywhere. Grants from the National Cancer Institute supporting just research pertaining to viruses and cancer here and abroad have risen to a total of about 160. This is an investment of over $5,600,000.

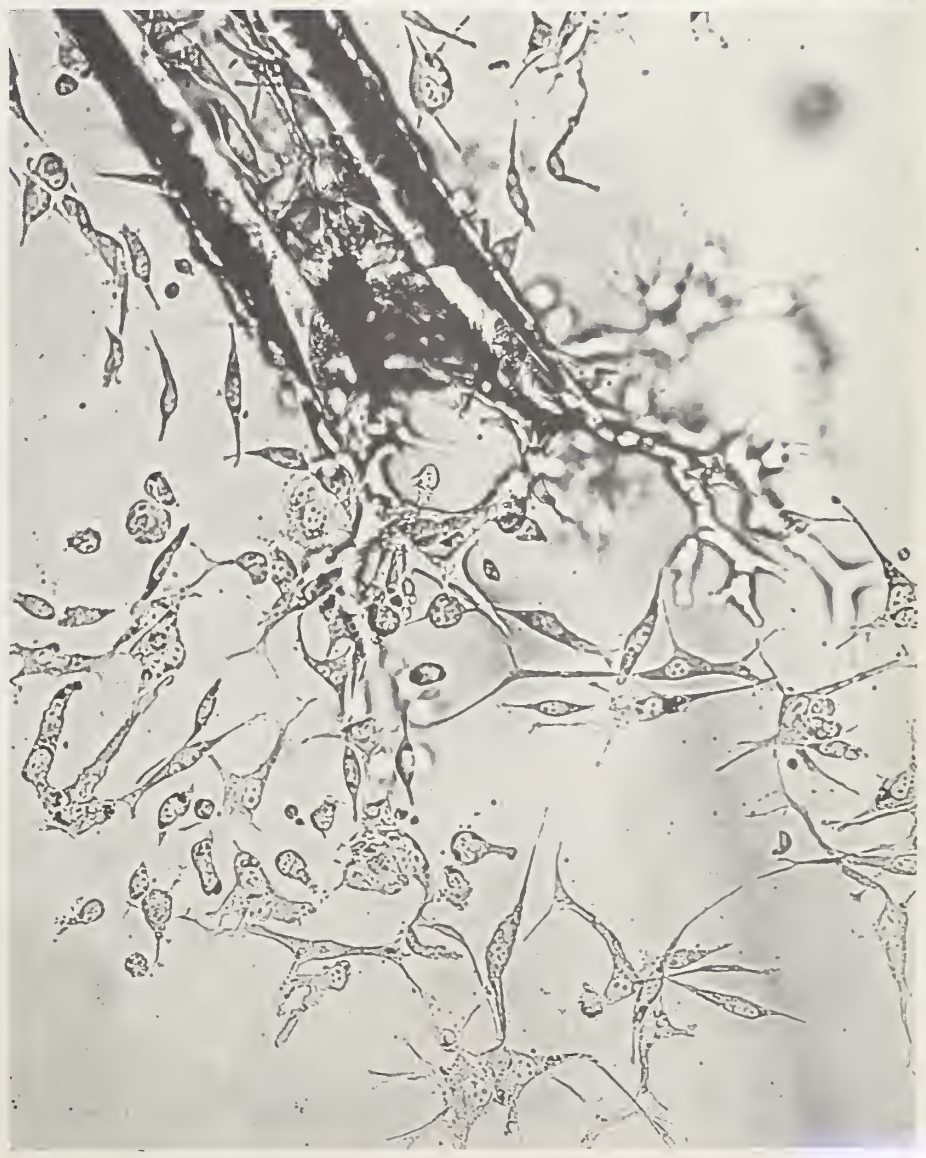
Meanwhile, cancer, a wily and many-faced foe, continues its implacable war against mankind. In the full day a dedicated scientist spends probing patiently with the electron microscope for virus in just one human sample, nearly 700 Americans will die of cancer.

And even for the diseases of man that are known to be caused by viruses there are almost no effective antivirus drugs.

Is progress really being made?

In the view of the scientists most deeply involved in the fight against cancer, the answer is yes. It is almost a truism of medicine that understanding the cause of a disease opens the road sooner or later to some form of control. It is this hope that is now mobilizing the virus specialists against cancer.

ELECTRON MICROSCOPES such as the one shown (right, above) can magnify objects up to 150,000 times. They are used to study the minute structures of cells and viruses.



CANCER CELLS (below, right) are shown in this microphotograph as irregularly shaped objects. This colony of cells grew from a single cancer cell planted in a glass tube, from which they have spread.

Hamsters Yield Clues to Causes of Tooth Decay

Dental researchers identify bacteria causing caries in experimental animals; NIH uses germfree techniques in nutrition, infectious disease and dental studies.

By HAROLD M. SCHMECK, Jr.

THERE is a family of hamsters in Bethesda, Md., that has had no tooth decay since 1957.

They have been thus blessed, not because of any inborn genetic trait, nor because of diet, but apparently because of something that happened to the maternal founder of their family tree. She was given enough penicillin to free her mouth completely of certain types of bacteria.

Those among her descendants who have been kept away from the same bacteria have been virtually free of tooth decay ever since. Those exposed have had cavities.

The family constitutes part of the evidence built up by scientists at the National Institute of Dental Research to show that tooth decay is a transmissible, bacteria-caused disease.

In related research "decay-resistant" breeds of hamsters have been given rampant tooth decay simply by exposing them to the germs normal to the mouths of other hamsters known to be "decay prone." Diets calculated to produce tooth decay failed to do so when the hamsters were kept free of some bacteria even though their mouths were far from being germ-free.

Scientists at Notre Dame University's Lobund Institute, a pioneer center for the study of germ-free animals, long ago showed that germ-free rats would not develop tooth decay.

LEADERS in the recent research at the National Institute of Dental Research have been Dr. Paul H. Keyes and Dr. Robert J. Fitzgerald. The concept that their research supports has revolutionary implications.

That bacteria play a role in dental decay is far from a new idea. In fact it had been thought that almost any bacteria capable of fermenting the carbohydrate in food would produce decay. In the animals studied at the institute in Bethesda, however, it is not just any bacteria, nor even just any good acid-producing bacteria, but certain specific microbes that appear to be to blame.

"It really does suggest that dental caries [decay] in humans might be the result of one, or at least a few, specific bacteria," said Dr. Francis A. Arnold, Jr., director of the institute, during a recent interview in Bethesda.

Dr. Keyes and Dr. Fitzgerald have found some of their most persuasive evidence in the mouths of syrian hamsters. Some of the little rodents are known to suffer from dental decay while others appear to be relatively free of it. The institute scientists believe that the difference lies in the microbes that grow normally in the animals' mouths.

They tested decay-free hamsters by putting into their mouths individual germ types that had been taken from the mouths of other hamsters suffering [illegible]inous tooth decay.

HAMSTER'S TEETH in upper photo have no cavities because they were kept free of bacteria. Lower photo shows extensive cavities in animal inoculated with pure cultures of streptococcus germs isolated from another hamster's decayed tooth.

Some eighteen kinds of bacteria, several of them copious producers of acid, generated no cavities.

THE bacteria that did produce decay were a group of five strains of streptococci all closely related chemically. A different streptococcus that had been found capable of producing tooth decay in germ-free rats did no damage to the hamster teeth.

Though the finger of suspicion thus seems to point toward streptococci, which are among the most common bacteria that afflict man, the evidence at least hints that different species may be susceptible to the tooth-destroying activities of different specific bacteria.

Both the streptococci that cause tooth decay in hamsters and the strain that brings cavities to the germ-free rat appear to be hitherto unidentified and unclassified strains. They are not closely like the common varieties that cause infections in man. They are not easily transmissible from one animal to another.

Many different bacteria normally inhabit the mouths of men and animals. It would be difficult indeed to prove that one type alone was the decay-producer for a given species, even if this were true, but the research evidence certainly seems to point to the few rather than the many.

THE hamster studies appear to show that the decay-producers in the bacterial "flora" are not so ubiquitous as had been thought by many scientists. It is possible that some animals just do not have the right organisms, Dr. Keyes said.

It is also apparent that the make-up of the bacterial flora may change with changes in diet or with the other conditions of an experiment. All these considerations are important to research. They might force revision of many of the interpretations that have been made from studies over the years, the scientists believe.

Looking forward, the findings also appear to have important implications.

Having apparently found single organisms that will cause tooth decay and others that will not, scientists may now cross-examine the decay producers to find out just what there is about them that does the job. Acid production presumably is an important factor in this, Dr. Keyes and Dr. Fitzgerald said, but there must also be an unknown factor.

It is for this that scientists can now search. If something characteristic of decay producers is found in animal studies, the bacteria in the mouths of men can then be searched for the same trait.

In such detailed bacteriologic studies of animals, the use of germ-free animals appears almost ideal.

"With the germ-free animals we hope to get a blow-by-blow documented account of what happens in dental decay," Dr. Fitzgerald said. "We hope to work out the complete life history of the diseases."

They plan to see if individual bacterial types alone will produce dental decay; whether two different species may sometimes do the job more effectively than one and, conversely, whether some bacteria might actually inhibit the decay-producing activities of others.

The matter of thinking of tooth decay as a disease leads inevitably to certain further thoughts, the scientists said. Customarily a bacterial disease is treated either by controlling or eradicating the organisms that cause it.

Do such specific organisms exist for human dental decay? If so, could they be found and eliminated? Presently these questions cannot be answered.

The evidence that streptococci are involved in tooth decay in two species makes the same family of bacteria a logical target for study in humans.

For some years children with rheumatic fever have been treated with penicillin over relatively long periods of time to forestall repeated attacks of the disease. One type of streptococcus is considered a causative agent in this disease and penicillin is usually effective against streptococci.

amsters Yield ues to Causes Tooth Decay

lans are now being considered to dy the dental health of children who e undergone such a long-term peni- in regimen to see if the suppression streptococci bacteria has had any nonstrable effect on their tooth decay.

HE National Institutes of Health e neither the oldest nor the largest ter of germ-free research, but their entists are pursuing studies in the d with a wide variety of objectives. To research workers at the National stitute of Arthritis and Metabolic seases a prime interest is in nutrition dies. Bacteria normally inhabit the gestive tracts of all animals and men. e they harmful? Are they useful? e there some of each kind?

Questions stemming from these basic es are being attacked in research led the institute's director, Dr. Floyd S. ft.

One such line of research has made it ar, over the last few years, that, in ts, intestinal bacteria are an impor- nt source of an essential vitamin, folic id, that is needed in normal metab- ism. There is evidence indicating that e same may be true in humans.

"Each of us apparently carries ound a very important vitamin fac- ry all the time," Dr. Daft remarked. He said current research was trying determine which bacteria are the ain contributors in this effort.

In another project scientists found at germ-free animals could develop rrhosis of the liver, thus seriously eakening the theory that the condition ight be of bacterial origin.

The largest germ-free animal facility the institutes is directed by Dr. Wal- r L. Newton in the Institute of Allergy nd Infectious Diseases. His unit is arrying on a wide variety of studies nbracing the specialties of virology, acteriology and parasitology as well as eneral biological problems.

In this laboratory Dr. Newton has fteen gleaming tanks in which hun- reds of small animals are born into a erm-free world and, in some cases, live ut their entire lives without ever en- ountering the normal complement of erms with which ordinary living things ust cope. The animals can be handled, ed and, if necessary, autopsied without ver being taken from the germ-free rea.

ACH tank is big enough to house 00 mice or a smaller number of larger nimals. Also used in the research are uinea pigs and, sometimes, chickens. ats will be introduced soon.

Although maintaining animals germ- ree over a long period of time is an xacting business, the institute mouse olony has been maintained for three ears with no unintentional contami- nation.

One of the laboratory's main interests in the role that ordinary contamina- ion plays in a variety of disease proc-

SAM THE HAMSTER, whose brothers, sisters, uncles and cousins participated in the research project which demonstrated that certain bacteria cause tooth decay, puts on an act of his own as he tries to escape from a beaker on a laboratory bench. Sam isn't one of the germfree hamsters. His teeth are quite likely to develop cavities, but he likes the relative freedom he has in the laboratory, denied to his cousins in the germfree tanks.

esses. An intestinal infection, for instance, is really a complex interrelationship between an infecting organism, the normal "flora" and the response of the "host"—the infected animal or person.

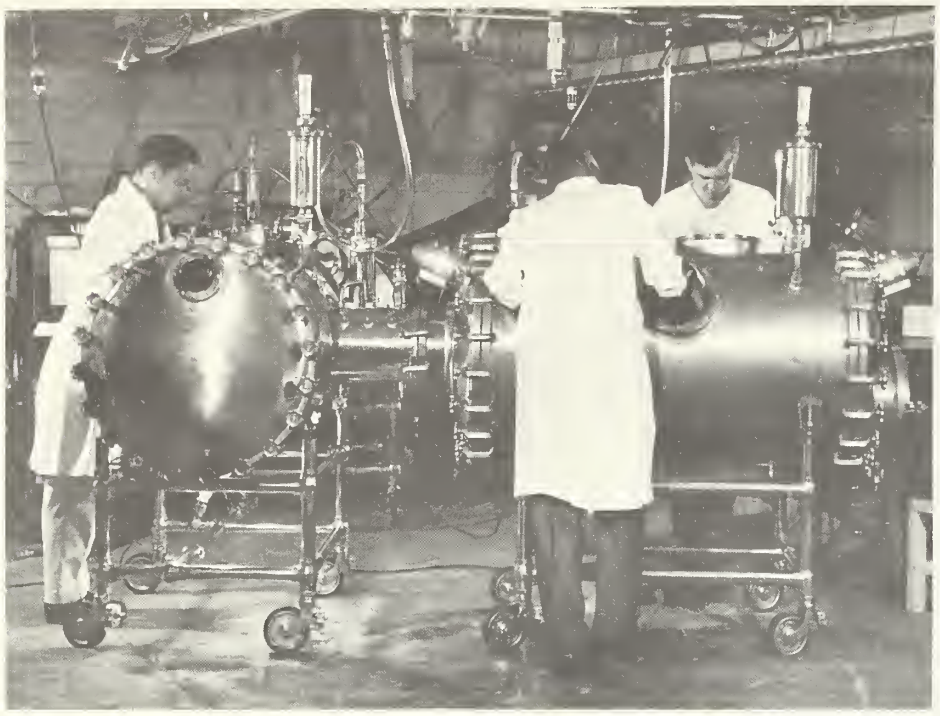
"We have been able to pick apart some of the host-organism relationships," Dr. Newton observed. The scientists have also been able to detect some of the subtle variations in germ-animal interaction that could not be detected in ordinary animals.

They have also found, for example, that some microscopic parasites that normally infect only one species will cross species lines in germ-free animals.

The great French scientist Louis Pasteur once predicted that an animal could not long survive in a totally germ-free state. Thousands of animals, free of all microbes with the possible exception of viruses, have lived to prove him wrong. The research they have made possible, however, has amply vindicated Pasteur's further suggestion that the germ-free state merited thorough study.

Hamsters Yield Clues to Causes of Tooth Decay

Although several different types of tanks or "isolators" are used in germfree studies at the National Institutes of Health, the type pictured on this page was developed at the Lobund Institute of Notre Dame University, pioneer center for the study of germfree animals. Animals shown are white rats.



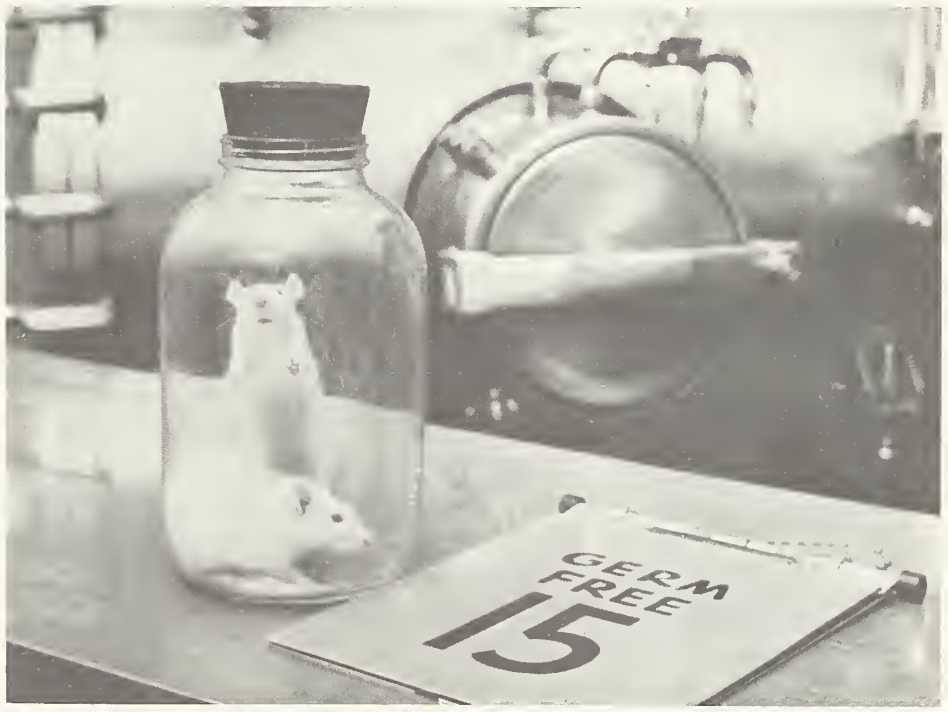
RATS IN JAR are placed in double-doored sterilizer of tank into which they are being transferred. Outer door (shown open) can be opened only from outside. Inner door (not visible) can be opened only from inside tank.

Above

GERMFREE ANIMALS are obtained by surgery (caesarean section) from mothers in germfree tank at right, then transferred to the connecting rearing tank at left. Germfree animals can also be obtained by transfer from one germfree enclosure to another or by natural birth from germfree animals within a germfree enclosure.

Below

TECHNICIAN, WORKING with animals, inside germfree tank, has his arms encased in rubber gauntlets sealed into portholes. He can thus reach in to perform all necessary activities without fear of introducing contamination into germfree atmosphere of tank.



Left

TWO GERMFREE RATS in the process of transfer from one tank to another are contained in large jar which was sterile both inside and outside before it was removed from tank. Still sterile inside, the jar will be passed through a sterilizing bath into another tank. (See photo above.)

Below

INSIDE THE TANK, a germfree rat's mouth is swabbed by a scientist taking a sample for analysis. Animals are kept in individual round cages in tank, which is supplied with a constant flow of pure air, electric lights, and stores of sterilized food and water. Worker wears cotton gloves over the rubber gauntlets attached to tank to minimize danger of puncture. Even a slight puncture of the rubber would lead to contamination of the tank and ruin the experiment.

CHNICIAN SEPARATES BIOCHEMICAL substances by means of exchange resins.

Biochemical Detectives Make Gains

Mental health research yields clue to role of important hormone; new diagnostic test for rare hereditary disease makes possible prompt treatment to halt mental deterioration.

By HAROLD M. SCHMECK, Jr.

IN a certain chemical sense, epinephrine is the stuff of which excitement is made.

It is an "emergency" hormone, better known by its old trade name, adrenalin. The body produces it in abundance when a person is angry, afraid or in the throes of drastic physical exertion.

It raises blood pressure, speeds the heart's action and generally prepares the body for combat or flight.

Its close relative, nor-epinephrine, is also involved in this call to arms and has other important functions in the nervous system.

But epinephrine is as notable for the secrets it still guards as those it has given up to science.

Almost all drugs that act on the mind apparently affect epinephrine's use in the body. Yet the role of this substance and its close relatives in mental health and illness is still obscure.

A REASON for the bafflement has been ignorance concerning the chemical fate of most epinephrine made by the body.

It is produced by the adrenal glands, and apparently also in the brain. But until recently, only about 3 per cent of the total output could be accounted for. What the body does with the rest has been a matter of controversy for half a century.

This circumstance and a rare type of tumor affecting the adrenal glands have set the stage for a biochemical detective story on which modern medical research thrives.

When adrenal glands are afflicted with such a tumor, the body produces enormous amounts of epinephrine. About four years ago a scientist at the University of Utah, Dr. M. D. Armstrong, found in the midst of this excess another chemical previously unknown.

In chemical structure it was like epinephrine, but there was a difference. It had a characteristic cluster of atoms, called a methyl group, in a most uncharacteristic spot.

Epinephrine has a methyl group—a cluster of one carbon and three hydrogen atoms—in a different position, but nor-epinephrine has none.

SCIENTISTS at the National Institute of Mental Health recognized a clue. They deduced that the new substance was a derivative of epinephrine. They also deduced the steps that lay between the original product and the new one.

Their line of deductions called for another "suspect"—an intermediate product—which had never been found.

The scientists injected volunteers with excessive amounts of epinephrine. In the chemical debris from this excess they found the missing product.

Later, they found the specific enzyme that transfers the important methyl group from one place to another. Painstakingly they worked out the complex story.

"The decisive experiment took a couple of hours," said Dr. Julius Axelrod, leader of the research group, during a recent interview in Bethesda, Md. "Working out all the details afterward took three years."

Although only 3 per cent of the epinephrine produced in the body could be accounted for previously, 98 per cent could be traced now. Transferring the methyl group was a critical factor in the body's use and disposal of the circulating epinephrine.

Much of the epinephrine was found to be held in tissues in an inactive form, Dr. Axelrod explained. The nervous system liberates it in an active form when and where needed.

THE ability to trace epinephrine's total course through the body has been put to important use. This research, in which normal volunteers and mental patients were used, seems to have weakened a major modern theory concerning schizophrenia.

The theory holds that this serious form of mental illness results from a chemical aberration in the body's use of epinephrine. While only a negligible amount of the body's total production could be traced, the theory could not adequately be tested.

Armed with the biochemical techniques for studying the whole picture, however, Drs. Elwood H. LaBrosse, Jay

(*Continued on page 20*)

Biochemical Detectives Make Gains

(*Continued from page 19*)

D. Mann and Seymour S. Kety made such a test.

In a series of experiments, described by the institute as "definitive," they compared the patterns of epinephrine's use and disposal in normal persons and schizophrenic patients. No differences that seemed likely to be of importance could be discerned.

Their findings "argue against the likelihood that a defect in metabolism of circulating epinephrine accompanies schizophrenia," they reported.

But it is unlikely that the story will end here.

One tantalizing clue, still to be pursued, involves again the clusters of atoms called methyl groups. These figure also in the structure of several drugs that produce hallucinations in man—dimethyltryptamine, LSD and the "vision"-producing substance that Mexican Indians have long obtained from certain mushrooms.

These drugs have structural similarities to epinephrine and nor-epinephrine. But unlike the two body products, they seem to have two characteristic methyl groups in their structure.

Only recently Dr. Axelrod and his colleagues have found that the adrenal gland can also produce small amounts of compounds that have two methyl groups arranged in positions suggestive of the hallucination-producing drugs. What this finding means is still unknown, but it invites speculation.

A different sort of detective story is being pursued in a laboratory only a few floors from Dr. Axelrod's in the National Institutes of Health Clinical Center in Bethesda.

This research has to do, literally, with the threads of human destiny.

These are man's chromosomes. Under the microscope they appear as bits of string often arranged like twisted X's.

The chromosomes carry genetic instructions from one generation to the next in all living things. Each cell that divides and multiplies has a set of chromosomes, which it passes on to its daughters so that they can become replicas of the parent.

In terms of a whole being such as a man, the chromosomes pass on instructions that the growing body translates in terms of color of eyes, shape of nose and a multitude of more important things.

The nature and functions of these agents of heredity have long been known, but the chromosomes of human cells have always been much more difficult to observe and study under the microscope than those of other species.

THE task has been so difficult that it was only in 1956 that the chromosomes of human cells were counted correctly for the first time.

It had been thought that the normal complement in human body cells was forty-eight. The development of new techniques for preparing the strands for microscopic viewing gave scientists a better look, and it was found that the correct number was forty-six.

The scientist credited largely for this revolution is Dr. J. H. Tjio, who has since become a staff member of the National Institute of Allergy and Infectious Diseases.

He is continuing his studies of human chromosomes for reasons intimately related to some of man's most baffling and tragic diseases.

Some diseases are known to stem from defects in the machinery by which a cell passes on instructions to the next generation of cells.

Some defects may be inherited, others result from accidents before birth or causes yet unproven. But in either case it is logical to expect that such defects may show themselves in the chromosomes.

It is for such evidence that Dr. Tjio, like scientists at many other institutions, is searching.

One particular area of search is in the bone-marrow cells of leukemia patients. Blood cells are formed in the bone marrow, and in leukemia, a form of cancer, the white blood cells are abnormally numerous.

SO far Dr. Tjio has studied the marrow cells of more than sixty leukemia patients. Though no definable pattern has yet emerged, one finding has been consistent, he said.

Glaring abnormalities are frequently found in cells of patients near death from the disease. It seems to suggest that the changes may be a result, rather than a cause, of the disease process.

Many biochemical detective stories, basically so important to medical science, are hard to relate directly to the relief or prevention of human suffering. One exception is a rare hereditary disease called phenylketonuria, or PKU.

Its effects stem from an abnormality in the way the body handles phenylalanine, a basic building block of protein that man must obtain from his diet.

The consequence of this abnormality in an infant is progressive and apparently irrevocable mental deterioration.

Within twenty-five years, scientists have discovered the disease, its basic cause, a way of preventing much of its tragic effect (by strict control of diet in the very young victim, and a simple test by which the ailment can be found early.

CHILD CHEERFULLY cooperates to supply a few drops of blood for diagnostic test.

Like most medical success stories, this one's roots are international. Many scientists and institutions have contributed, and the story is still unfinished.

Staff members and grantees of the National Institutes of Health have made important contributions to this progress, including the discovery that it is the lack of only a single enzyme that puts the PKU infant in such terrible jeopardy.

A recent contribution is a new test for the disease, requiring only a drop of blood from the finger tip. Its importance is that it can be done routinely during an infant's first day of life.

Previously available tests, though simple, could not be done so early, and sometimes had to be delayed weeks or months. Yet, it has been estimated that a child's I.Q. may drop five points for every ten weeks after birth that treatment is delayed.

The ailment is rare, but its importance is not to be measured in terms of numbers alone. It is one of those disorders that demonstrate the profound effects a subtle, hardly detectable biochemical derangement can produce.

The study of PKU promises to help uncover the causes of other hereditary disorders, particularly the basis for other types of mental deficiency.

The disorder thus exemplifies many so-called molecular diseases, and the rewards that may accrue from the ceaseless probing of these points on the far frontiers of modern biomedical research.

SCIENTIST CONSTRUCTS molecular model of a body chemical under study.

WHAT IS IT? Photograph on back cover shows, impaled upon an instrument used in laboratory studies, the lens removed from the eye of a healthy eight-weeks-old rabbit used in studies of the physics of light transmission. It is focused on a section of the ruler in the background. Turn the page upside down and you should be able to read the word "apparatus" through the lens. The studies have been undertaken at NIH to gain a better understanding of the causes and effects of lens opacities (cataracts) of the eye. The large white ring horizontal to the ring upon which the lens is mounted acts as the cap of a cylinder containing tissue culture fluid in which lens is kept immersed to maintain it in good condition. (Photograph is enlarged.)

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THE NIH CLINICAL CENTER looms in the distance, as seen through an archway and beyond the garden wall on the grounds of one of the mansions built when the area now occupied by NIH was private property. The view is fro[illegible] of Clinical Center is shown in picture on page 2.

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